REMARKS

Claims 1, 6 and 9-11 currently are pending in the application. In view of the following remarks, Applicants believe that all the rejections are in condition for withdrawal and that all pending claims 1, 6 and 9-11 are in condition for allowance.

The Present Invention

The present invention as claimed in claim 1 is directed to a method of enhancing an immune response to an antigen in a mammal comprising administering to the mammal lymphocyte conditioned media derived from naïve T cells cultured with antiCD3- and CD28-coated beads in combination with a vaccine of the antigen.

35 U.S.C. § 103 Rejection of Claims 1 and 9-11

Claims 1 and 9-11 are rejected under 35 U.S.C. § 103(a) as being obvious over Baxevanis et al. in view of Setaluri et al. and Mengozzi et al. The Examiner asserts that, although Baxevanis et al. are silent as to the antigen to be administered with the activated PBMC supernatant, Setaluri et al. describe the dosage calculation and the time schedule and route of administration, and Mengozzi et al. disclose antiCD3/CD28-coated beads for *ex vivo* stimulation of T cells.

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a *prima facie* case of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. *Id. In re Fine,* 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious *unless the prior art suggests the desirability of the modification* (emphasis added). *In re Fritch*, 23 U.S.P.Q.2d at 1784; *In re Laskowski*, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); *In re Gordon,* 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

As described above, the claimed invention is directed to a method of enhancing an immune response to an antigen in a mammal comprising administering to the mammal lymphocyte conditioned media derived from naïve T cells cultured with antiCD3- and CD28-coated beads in combination with a vaccine of the antigen.

In contrast, Baxevanis et al. disclose a method of adding supernatants collected from donor-derived PBMCs stimulated with anti-CD3 monoclonal antibody, but, as acknowledged

by the Examiner, do not teach or suggest anti-CD3/CD28 beads for T cell activation and are silent on the antigen to be administered with the activated PBMC supernatant.

With respect to Setalauri et al., this reference is directed to the detection of microtubule associated protein-2 (MAP-2) as a marker to determine the metastatic potential of a tumor, including tumors derived from the neural crest such as melanomas, gliomas, Schwanomas, chromocytomas and small cell lung cancer. Additionally, Setalauri et al. disclose the use of MAP-2 to prevent tumor progression by increasing levels of MAP-2 protein in cells (column 2, paragraph 17). Thus, the disclosure of Setalauri et al. relates specifically to MAP-2 expression and the finding that decreasing MAP-2 expression may prevent tumor progression in metastatic cancer cells. Furthermore, the assertion that Setalauri et al. disclose the administration of a tumor antigen is irrelevant to the claimed invention. As described hereinbefore, the present invention as claimed in claim 1 is directed to the administration of a vaccine of a particular antigen (and not to a marker for a cancer antigen), which is administered in combination with lymphocyte conditioned media derived from naïve T cells cultured with antiCD3- and antiCD28-coated beads to enhance an immune response in a mammal (and not to the detection of a biomarker, i.e., MAP-2, to determine the metastatic potential of a tumor).

Applicants submit, therefore, that the teaching of Setalauri et al., i.e., that decreasing MAP-2 expression may prevent tumor progression in metastatic cancer cells; a particular dosage calculation; and the timing and route of administration of an antigen, would not motivate one skilled in the art to combine this teaching with the teaching of Baxevanis et al., which discloses a method of adding supernatants collected from donor-derived PBMCs stimulated with anti-CD3 monoclonal antibody.

Furthermore, Applicants submit that if one skilled in the art were attempting to combine the teaching of Baxevanis et al. with the teaching of Setaluri et al. in the manner in which the Examiner has suggested, one could not do so without substantial destruction of the independent teachings of the references in a manner not suggested by the two references. Moreover, even if one skilled in the art, with the improper use of hindsight, attempted to forcefit these fragmentary teachings into the combination suggested by the Examiner, one still would not have the teachings of Applicants' invention as currently claimed.

With respect to Mengozzi et al., this reference discloses coating beads with anti-CD3/CD28 for *ex vivo* stimulation of T cells. As such, therefore, Mengozzi et al. do not cure the deficiencies of Baxevanis et al. and Setalauri et al., described above, namely, the lack of a showing of an objective teaching in the prior art, or knowledge generally available to one of

ordinary skill in the art, which would lead one skilled in the art to combine the relevant teachings of Baxevanis et al. with Setaluri et al. in the manner suggested by the Examiner.

Applicants respectfully submit, therefore, that Baxevanis et al., Setaluri et al. and/or Mengozzi et al. neither teaches nor suggests the claimed invention as claimed in claim 1. The features of dependent claims 9-11 are not asserted as independently establishing patentability apart from claim 1 from which they depend. Thus, claims 9-11 also are neither taught nor suggested by Baxevanis et al., Setaluri et al. and/or Mengozzi et al. Applicants therefore respectfully request withdrawal of the rejection of claims 1 and 9-11.

35 U.S.C. § 103 Rejection of Claims 1 and 6

Claims 1 and 6 are rejected under 35 U.S.C. § 103(a) as being obvious over Baxevanis et al. in view of Meidenbauer et al. and Mengozzi et al. The Examiner asserts that Meidenbauer et al. disclose administering a PSA-based vaccine in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) to induce a cellular immune response to human PSA predominantly mediated by T lymphocytes. The Examiner acknowledges that Meidenbauer et al. do not disclose administering LCM derived from naïve T cells cultured with antiCD3- and antiCD28-coated beads.

The disclosures of Baxevanis et al. and Mengozzi et al. are as described hereinabove.

Meidenbauer et al. disclose the use of a vaccine for therapy of prostate cancer which consists of recombinant prostate specific antigen (PSA) formulated into liposomes (abstract). Meidenbauer et al. also disclose administering this liposome-encapsulated vaccine in combination with GM-CSF (abstract).

Nowhere do Meidenbauer et al. teach or suggest administering lymphocyte conditioned media derived from naïve T cells cultured with antiCD3- and CD28-coated beads in combination with a vaccine of an antigen to a mammal to enhance the immune response to the antigen. Rather, Meidenbauer et al. teach the use of a vaccine formulated into liposomes with or without the use of GM-CSF.

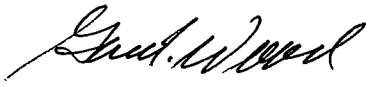
Moreover and, more importantly, contrary to the Examiner's assertion that a PSA-based vaccine in combination with GM-CSF induces a cellular immune response to human PSA predominantly mediated by T lymphocytes, this reference actually teaches away from the use of a vaccine in combination with GM-CSF. Specifically, Meidenbauer et al. disclose the use of "PSA formulated in the lipid emulsion" which "generated cellular responses in all patients, whereas that using a concomitant treatment with GM-CSF generated a response only in 3/5 patients" (page 98, second paragraph). Thus, Applicants submit that one skilled in the

art would not be motivated to combine a vaccine with GM-CSF and expect to get an efficaciously enhanced immune response in prostate cancer patients.

Furthermore, the critical inventive feature of the present invention, as claimed in claim 1, inheres in the unexpected finding that a vaccine per se (not encapsulated in liposomes) in combination with lymphocyte conditioned media derived from naïve T cells cultured with antiCD3- and CD28-coated beads enhances the immune response in a mammal. Thus, Applicants submit that one skilled in the art would not derive the claimed invention from combining the teachings of Baxevanis et al. in view of Meidenbauer et al. and Mengozzi et al. Applicants, therefore, submit that the teachings of Baxevanis et al. in view of Meidenbauer et al. and Mengozzi et al., either alone or in combination, do not teach or suggest the present invention as claimed in claims 1 and 6. Applicants therefore respectfully request withdrawal of the rejection of claims 1 and 6.

In view of the foregoing remarks, it is respectfully submitted that all pending claims 1, 6 and 9-11 in the present application are distinguishable from the cited prior art. Accordingly, reconsideration and withdrawal of the rejections and an early Notice of Allowance are respectfully requested.

Respectfully submitted,



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